Acute Nutritional Ketosis in VLCAD Deficiency: testing the metabolic basis for therapeutic use

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metabolism disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON44949

Source
ToetsingOnline

Brief title
Acute Nutritional Ketosis in VLCADD

Condition

- Metabolism disorders NEC

Synonym
metabolic disease, VLCADD

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: metabolism, nutritional ketosis, VLCADD

Outcome measures

Primary outcome

To investigate:

1. the potential of a novel dietary substrate preparation to enhance muscle

mitochondrial function in VLCADD via acute nutritional ketosis.

2. if tri-citric acid cycle substrate supply in muscle of patients with

VLCADDis boosted by acute nutritional ketosis.

Secondary outcome

nvt

Study description

Background summary

Very Long-Chain Acyl-CoA Dehydrogenase deficiency (VLCADD) is an inborn error of fatty acid metabolism with a broad clinical presentation ranging from infant fatality to exercise intolerance and elevated risk of exertional rhabdomyolysis in symptomatic adult patients. We recently obtained evidence that these symptoms are in part due to a lower energetic efficiency of upper leg muscle fibers that aggravates reliance on carbohydrate stores in this disease, rendering the organ vulnerable to an exertional energy crisis. While no effective treatment has been available for VLCADD, it has long been proposed that nutritional ketosis (NK) could be highly beneficial to patients. Amongst others, ketone bodies could take on the role of primary energy source in exercising muscle. The problem has been that, until now, no vehicle for establishing NK in humans without undesired side effects has been available. A breakthrough has finally been achieved by collaborator Kieran Clarke in Oxford whose team has recently produced an edible ketone ester that can achieve acute

NK in human subjects via oral ingestion without any undesired side-effects. It was found that the ketone ester produced significant physical performance enhancement in rodents and human athletes. The effect has been attributed to enhanced muscle mitochondrial function in addition to glycogen sparing. Here, we will investigate if acute NK in adult symptomatic VLCAD deficient patients can boost muscle mitochondrial function in vivo. If so, a rational basis will have been established for therapeutic use in this metabolic myopathy. As such, this study constitutes a vital first step towards possible validation of an effective treatment for patients with VLCADD that may improve the quality of life including an active lifestyle with overall health benefits.

Study objective

To test if acute NK boosts muscle mitochondrial function in vivo in patients with VLCADD in order to establish a rational basis for therapeutic use in this disorder.
A secondary objective is to gather data to test the working hypothesis that the positive effect of acute NK on muscle mitochondrial function results from enhanced substrate supply to the tricyclic acid (TCA) cycle.

Study design

A randomised, blinded, placebo controlled, 2-way cross over trial.

Study burden and risks

The burden of collecting tissue samples from the quadriceps muscle by microbiopsy is rated as moderate. As such, this intervention will only be performed on a voluntary basis. The burden of microbiopsy is considered justifiable.

In the short, maximum exercise test in session 1 anaerobic derived energy will be used. As patients with VLCADD do not have a problem in glycolysis, the burden for this test will be nihil.
The endurance test at submaximal level (session 2 and 3) might induce muscle pain temporarily. The burden for patients is classified as minimal and patients will be monitored accordingly during the study period.

Blood will be drawn intravenously from patients; this implies a minimal burden.

The safety of the nutritional drinks that will be administered and the expected acute, transient mild ketosis has been thoroughly tested and documented in healthy subjects. The drink has been designated as Generally Recognized as Safe by the Federal Drug Administration of the United States allowing it to be used as a foodstuff in the USA. No particular risk for VLCADD patients is expected with respect to oral ingestion of the ketone ester since its metabolites are

natural, organic compounds.

Concerning the MRI-scanner, participants will be exposed to a field strength of 3 Tesla and scanner noise. Thus far, there is no evidence to suggest that exposing humans to a magnetic field of this strenght has a negative influence on health. With regard to the noise earplugs and headphones will be provided.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

* Confirmed VLCADD by genetic profiling
* age: 16-65

Exclusion criteria

* contra indications for MRI studies (assessed by standardised questionnaire as previously used in METc 08-267/K. Such as metal implants, vascular clips, eye-implants, metal particles in the eye, tattoos containing iron oxide, suspected pregnancy, refusal to be informed of strucural brain abnormalities that could be detected)
* inability to perform bicycle exercise.
* recent episode of rhabdomyolysis, or treatment for acute renal failure in the past 2 months.
* intercurrent illness which may influence exercise tolerance (anaemia, musculoskeletal injury, or other undiagnosed illness under investigation).
* known coronary artery disease, positive history for angina, or changes on ECG suggestive of previous ischaemia without a negative stress test.
* insulin-dependent diabetes mellitus.
* loss of, or an inability to give informed consent.
* pregnancy or current breastfeeding, or females not taking the oral contraceptive pill
* any other cause which in the opinion of the investigators, may affect the volunteers ability to participate in the study

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2016
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	24-03-2015
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-10-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL51222.042.14